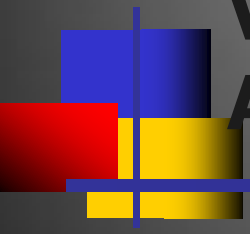
# A Phase I Study to Evaluate the Safety and Immunogenicity of an Ebola DNA PLASMID Vaccine, VRC-EBODNA023-00-VP, & a Marburg DNA PLASMID Vaccine, VRC-MARDNA025-00-VP, in Healthy Adults



# Background

- Ebola and Marburg are filoviruses, known to induce hemorrhagic fever
- Both are large, negative-strand RNA viruses composed of 7 genes encoding proteins, including a single glycoprotein
- Transmission to humans is not yet fully understood, but likely includes incidental exposure to infected animals

# Background

- Human outbreaks of Ebola and Marburg hemorrhagic fever have only occurred in Africa;
- A previously unseen strain of Ebola caused an outbreak in imported laboratory nonhuman primates in Reston, VA in 1989;
- These viruses (and poaching) have pushed populations of wild gorillas to the brink of extinction in Western African countries

# Human Disease

- Brief incubation period, rapid onset of non-specific symptoms (fever, extreme fatigue, gastrointestinal complaints, abdominal pain, anorexia, headache, myalgias and/or arthralgias).
- More severe symptoms including hemorrhagic rash, epistaxis, mucosal bleeding, hematuria, hemoptysis, hematemesis, melena, conjunctival hemorrhage, tachypnea, confusion, somnolence, and hearing loss.
- High mortality (Case fatality rate 50% to 90% for Ebola, and 23-100% for Marburg) days after the onset of symptoms)

# Background

- Ease and frequency of air travel pose a potential threat of spread of human disease.
- Both listed by CDC as Category "A" Bioterrorism Agents,
  - "…organisms that pose a risk to national security because they can be easily disseminated or transmitted from person to person, result in high mortality rates, and have the potential for major public health impact; might cause public panic and social disruption; and require special action for public health preparedness."

# Goals

- Overall goal of the VRC filovirus vaccine development plan is to develop a regimen effective in preventing both Ebola and Marburg.
- In human survivors, both humoral and cellular immunity are detected, however, their relative contribution to protection is unknown
- Preclinical studies of classical whole-killed virions and live attenuated viruses and of recombinant gene-based vector approaches demonstrate partial protection in animals but no cell mediated immune responses

# Ebola Marburg DNA Vaccine Study

- Preclinical safety and immunogenicity data
- No human data on these 2 DNA vaccine candidates
- Human safety data from 8 other similar DNA vaccines -safe and well-tolerated in healthy adults ages 18-65 years old.

# Study objectives for Phase 1

- Hypothesis: each of the two recombinant DNA vaccines will be safe for human administration and elicit a humoral and T cell mediated immune response.

- Objectives:
  1. Evaluate the safety and tolerability of 3 (or 4) 4mg. doses of the investigational vaccines in healthy adults.
  2. Evaluate the immunogenicity of each study vaccine

# Study Design

- Open label First-in-human Phase I study to evaluate safety, tolerability, and immunogenicity of two recombinant DNA vaccines: one against Marburg virus infections and one against Ebola virus infections.

# Study vaccines

- VRC-MARDNA025-00-VP (Marburg DNA) is composed of one closed-circular DNA plasmid encoding for the glycoprotein (GP) from the Angola strain of Marburg.
- VRC-EBODNA023-00-VP (Ebola DNA WT) is composed of two closed-circular DNA plasmids, one encodes for GP from the Zaire strain and one encodes for GP from the Sudan-Gulu strain of Ebola.
- Volunteers *cannot* become infected with Ebola virus or Marburg virus from the vaccines.
- Each DNA vaccination will be given intramuscularly (IM) into the deltoid muscle using the Biojector® 2000 Needle-Free Injection Management System (Biojector).

# Study Sample

- 20 healthy adults, ages 18-60 years
- Enrolled into 2 groups of 10 subjects each. (No more than one 51-60 year old per group).
- Group 1 : Marburg DNA; Group 2: Ebola DNA WT
- Only one per day in each group up to 3 enrollments

# Inclusion criteria

- 18 to 60 years old
- Available for clinic follow-up through week 32
- Able to provide proof of identity
- Able, willing to complete consent process and AoU
- Willing to donate blood for storage for future research
- Good general health without clinically significant medical history
- Physical examination and laboratory results WNL
- Body mass index (BMI) less than 40 within prior 28 days
- Normal Hgb, WBC, Differential, platelets, ALT, serum creatinine, PT/ PTT
- Negative HIV, HBV, HCV
- Normal urinalysis
- For females- negative pregnancy test, and must either have no reproductive potential **or** be willing to be sexually inactive, **or** be willing to use contraception from 21 days before through wk 32

# Exclusion criteria

- Prior Investigational Ebola vaccine, Immunosuppressive medications, Blood products or Immunoglobulin within 60 days; investigational research agents within 30 days
- Medically indicated subunit or killed vaccines, (e.g. influenza, pneumococcal), or allergy treatment with antigen injections within 14 days of study vaccine; No live attenuated vaccines within 30 days
- History of serious adverse reactions to vaccines **or** allergic reaction to aminoglycoside antibiotics
- Current anti-TB prophylaxis or therapy
- Autoimmune disease or immunodeficiency, asthma, diabetes, thyroid disease, malignancy, bleeding disorder, seizure disorder, angioedema, uncontrolled hypertension
- Asplenia or functional asplenia
- Psychiatric condition that precludes compliance; past or present psychoses or bipolar disorder; disorder requiring lithium; or a history of suicide plan or attempt
- Any medical, psychiatric, social condition, occupational reason or other responsibility that, in the judgment of the investigator, is a contraindication to protocol participation or impairs a subject's ability to give informed consent

# Study procedures

- Study requires 9 clinic visits and 3 telephone follow-up contacts over 32 weeks
- Each subject to receive 3 injections of vaccine at least 21 days apart
- Protocol amendment - 4th injection for those who consent.
  - Follow up 4 visits and 1 phone contact over an additional 12 weeks

# Study Procedures

- 30 minute observation after each injection.
- Daily diary card of symptoms and temperature for 5 days
- Phone call to study nurse 1 day after injection.
- Clinic visit if rash or hives or a fever of $\geq$ 38.7˚C (101.7˚F) for more than 24 hours or difficulty in usual daily activities

# Study Procedures

- Clinic visits-
  - Health or medication changes or problems
  - Blood samples (2 to 9 TBSP per visit, study total about 970 ml)
  - Urine sample at some visits
  - Blood for genetics studies and HLA typing

# Payment

- $275 for vaccine injection visits
- $175 for clinic visits with blood draws
- $75 if no blood draw or injection
- Total possible $1875
- Pro-rated

- You are the IRB asked to review and approve this study
- What issues should be considered?

# Criteria for review

1) Collaborative partnership
2) Social Value
3) Scientific Validity
4) Fair Subject Selection
5) Favorable Risk-Benefit Ratio
6) Independent Review
7) Informed Consent
8) Respect for Enrolled Participants

1. Risks are minimized
   - Using procedures consistent with sound scientific design
   - Using procedures already planned for diagnosis or treatment
2. Risks are reasonable in relation to anticipated benefit and importance of the knowledge
3. Subject Selection is equitable
4. Informed consent is obtained from subject or LAR & documented
5. Plans for monitoring
6. Plans for protecting privacy and confidentiality

# IRB Actions

- Approve
- Approve with stipulations
- Defer
- Table
- Disapprove